Risks and Benefits of Tumor Necrosis Factor-α Inhibitors in the Management of Psoriatic Arthritis: Systematic Review and Metaanalysis of Randomized Controlled Trials

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ABSTRACT. ***Objective.*** To evaluate the efficacy and safety of tumor necrosis factor-α (TNF-α) inhibitors in the management of psoriatic arthritis (PsA).

Methods. We searched electronic databases to identify randomized controlled trials (RCT) of adalimumab, etanercept, and infliximab used in patients with PsA. Random effects metaanalysis was undertaken to produce pooled estimates of the relative risk, risk difference, or the weighted mean difference for efficacy and safety outcomes using Stata version 9.0.

Results. Six RCT met the inclusion criteria, including 982 patients. All 3 TNF-α inhibitors were significantly more effective than placebo on the basis of Psoriatic Arthritis Response Criteria (PsARC) and American College of Rheumatology response criteria ACR20, ACR50, and ACR70 ratings. There were no significant differences between TNF-α inhibitors and placebo in the proportions of patients experiencing withdrawal for any reason (RR 0.48, 95% CI 0.20–1.18), or withdrawal due to adverse events (RR 2.14, 95% CI 0.73–6.27), serious adverse events (RR 0.98, 95% CI 0.55–1.77), or upper respiratory tract infections (RR 0.91, 95% CI 0.65–1.28). Pooled rates for injection site reactions were significantly higher for adalimumab and etanercept than for placebo (RR 2.48, 95% CI 1.16–5.29), but there was no significant difference in the proportion of patients experiencing infusion reactions with infliximab (RR 1.03, 95% CI 0.48–2.20) compared against placebo. Indirect analysis did not demonstrate any significant differences between the TNF-α inhibitors.

Conclusion. TNF-α inhibitors are effective treatments for PsA with no important added risks associated with their short-term use. There is still a need for longterm risk-benefit assessment of using these drugs for the management of PsA. (First Release Mar 15 2008; J Rheumatol 2008;35:883–90)

Key Indexing Terms:
PSORIATIC ARTHRITIS TUMOR NECROSIS FACTOR-α INHIBITORS
ADALIMUMAB ETANERCEPT INFLIXIMAB METAANALYSIS

Psoriatic arthritis (PsA) is a chronic inflammatory condition occurring in 6%–39% of patients with psoriasis, which in turn affects 1%–2% of the general population[1-3]. It can be a destructive and occasionally disabling joint disease, and the severity of joint damage tends to increase progressively over time[4]. In addition to joint inflammation, patients frequently experience dactylitis, spondylitis, and enthesitis[5]. Psoriatic skin lesions can also cause skin irritation, soreness, and bleeding. The joint and skin components of the disease have a profound influence on the quality of life of patients with PsA, resulting in considerable physical and psychosocial morbidity[6]. It has been estimated that the total direct costs, including hospitalizations, doctors' visits, and drug and nondrug treatment, for patients with psoriasis and PsA are as high as $650 million in the US[7].

Traditionally, nonbiologic disease modifying antirheumatic drugs (DMARD) have been the mainstay of treatment to control moderate to severe disease activity in PsA. However, a Cochrane systematic review found that the only nonbiologic DMARD that have been shown to be effective in PsA were high-dose parenteral methotrexate and sulfasalazine[8]. Recently, leflunomide has also been found to be effective[9]. In addition, several tumor necrosis factor-α (TNF-α) inhibitors (adalimumab, etanercept, and infliximab) have recently been licensed for the management of PsA.

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The rationale for targeting TNF comes largely from studies showing that concentrations of this proinflammatory cytokine are elevated in the skin and joints of patients with PsA[10]. TNF-α acts in the early stages of the inflammatory process, inducing the expression of interleukin 2 (IL-2), interferon-γ receptors, proinflammatory cytokines (such as IL-1 and IL-12), and proinflammatory chemokines (such as IL-8), and stimulating T-cell activation[11]. A number of randomized controlled trials (RCT) have evaluated the use of TNF-α inhibitors in PsA. A review of treatments for PsA reported that evidence supports improvements in symptoms, physical function, quality of life, and radiographic progression with TNF-α inhibitors[12]. However, this review did not combine the results across different trials or examine the incidence of adverse events. The aim of our study therefore was to undertake a comprehensive review and metaanalysis of published RCT examining the efficacy and safety of TNF-α inhibitors in the management of PsA.

MATERIALS AND METHODS

We included double-blind RCT that compared the use of adalimumab, etanercept, or infliximab (used at licensed therapeutic dosages) against placebo or other active treatments in patients with at least 3 swollen joints and 3 tender or painful joints, and reported on efficacy and/or safety outcomes. For efficacy, the primary outcome measure was the American College of Rheumatology 20 (ACR20) response at 12–16 weeks. Efficacy measures also included the Psoriatic Arthritis Response Criteria (PsARC)[13,14]; the ACR50 and ACR70 scores[15]; and the Psoriasis Area Severity Index (PASI) 50, PASI 75, and PASI 90[16]. The Disability Index of the Health Assessment Questionnaire (HAQ-DI) was included to assess physical function, and we also included measures that assessed the impact on quality of life.

Safety outcomes included the proportions of patients experiencing upper respiratory tract infections, serious adverse events, and malignancies. We also examined the overall withdrawal rates from the trial, and withdrawals due to adverse events, as well as the proportions of patients experiencing injection site reactions, or infusion reactions in the case of infliximab.

Search strategy. RCT fulfilling the inclusion criteria were included, regardless of language or publication status. We systematically searched Medline, Embase, Cinahl, and the Cochrane controlled trials register from their respective inception dates to May 2007. In addition, we also searched the US Food and Drug Administration and European Medicines Evaluation Agency websites, and the reference lists of all retrieved reviews and trials to identify any additional eligible studies. An optimal search strategy for the identification of RCT that was developed by the Cochrane Collaboration was used[17]. This was supplemented with additional search terms, which included "biologic," the generic and brand names of each of the drugs ("adalimumab," "etanercept," and "infliximab"), "anti-TNF," and "psoriatic arthritis."

Data extraction. Two authors (AAS, DMA) independently extracted relevant outcome data from the retrieved trials, and any differences were resolved through discussion. For dichotomous data, frequencies in each group (intervention and control) that achieved the desired outcomes and the total number of patients that were treated were extracted in a tabular form; while for continuous data, the change in response from baseline, the standard deviation for the change, and the total number of patients intended to be treated for both the intervention and the control groups of each trial were extracted. The following data were also documented: study design, number of subjects, trial duration, blinding period, outcome measures used, and treatment regimen. Quality assessment of the included studies was conducted using the Jadad scale and scored out of a maximum of 5, with higher scores indicating better quality in the conduct or reporting of the trial[18]. There was no masking of trials for quality assessment. A minimum quality score of 2 was required for inclusion of each trial, which indicated blinding and randomization.

Data analysis. We conducted the efficacy analyses according to the outcome measure, TNF-α inhibitor used, and timepoint. For head to head comparisons, random-effects metaanalysis was performed to produce a pooled estimate of relative risk (RR), risk difference, or weighted mean difference (WMD) with 95% confidence intervals for each of the outcomes of interest using Stata version 9.0[19,20]. The random-effect model is commonly used when there is evidence of heterogeneity because it takes into account variability between studies, as well as within studies[21]. Homogeneity testing was performed to test for the suitability of combining the trials using the chi-square and I^2 tests[22]. For indirect comparisons between TNF-α inhibitors, we used the method adopted by Bucher, *et al*[23]. In the indirect comparisons, outcomes at Week 12 were used for adalimumab and etanercept while data at Weeks 14–16 were used for infliximab.

RESULTS

Study characteristics. In all, 6 randomized placebo-controlled parallel-group trials (RCT) met the inclusion criteria including 982 patients with PsA, as shown in Figure 1. The RCT lasted from 12 to 24 weeks' duration; 2 trials used adalimumab [40 mg subcutaneous (SC) every other week for 24 weeks][24,25], 2 trials used etanercept (25 mg SC twice/wk)[26,27], and 2 trials used infliximab (5 mg/kg)[28,29], as shown in Table 1. Table 2 summarizes key demographic characteristics of the participants included in the RCT.

Clinical efficacy. All 6 RCT reported results for ACR20,

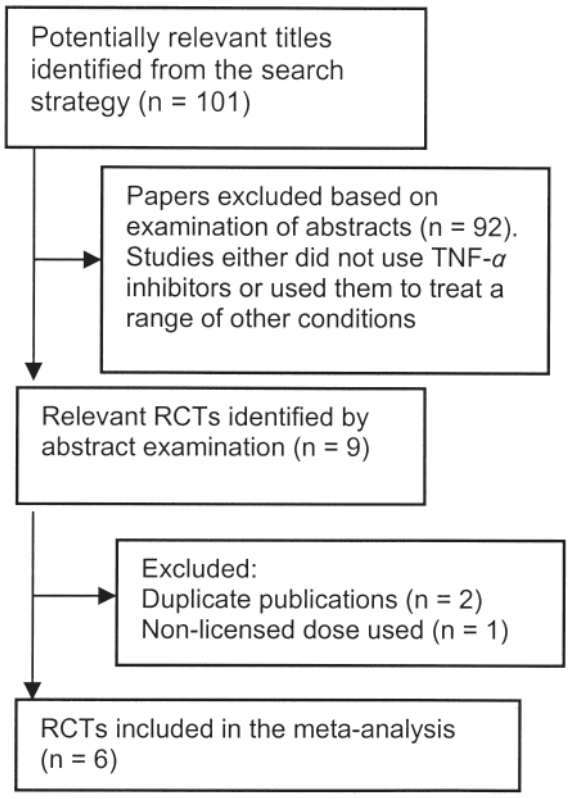

Figure 1. Selection of studies included in the analysis.

Table 1. Characteristics of randomized controlled trials.

Trial	Agent	Settings	Duration of Trial, wks	Licensed Intervention, no	No. of Controls	Quality Score[18]	Outcome Measures*
Mease[24] Gladman[32]	Adalimumab	50 sites in Europe, Australia, USA, Canada	24	40 mg SC every other week (n = 151)	162	3/5	ACR20, ACR50, ACR70, PsARC, PASI 50, PASI 75, PASI 90, HAQ-DI, SF-36, TSS and AE
Genovese[25]	Adalimumab	16 sites in USA, Canada	24	40 mg SC every other week (n = 51)	49	5/5	ACR20, ACR50, ACR70, PsARC, HAQ-DI, SF-36, TSS and AE
Mease[26] Mease[33]	Etanercept	NS	12	25 mg SC twice/week (n = 30)	30	5/5	PsARC, ACR20, ACR50, ACR70, HAQ-DI, and AE
Mease[27]	Etanercept	17 sites in USA	Blinded for 24 then open to 48	25 mg SC twice/week (n = 101)	104	4/5	ACR20, HAQ-DI, PsARC and AE
Antoni[28]	Infliximab	9 sites in Europe, USA, Canada	Blinded for 16 then cross over to 50	5 mg/kg at Weeks 0, 2, 6, 14 then every 8 weeks to Week 50 (n = 52)	52	4/5	ACR20, ACR50, ACR70, HAQ-DI, PsARC and AE
Antoni[29†] Kavanaugh[29]	Infliximab	36 sites in USA, Europe, Canada	16 then early escape to 24	5 mg/kg at Weeks 0, 2, 6, 14, 22 (n = 100)	100	4/5	ACR20, ACR50, ACR70, PASI 50, PASI 75, PASI 90, HAQ-DI, PsARC, SF-36, and AE

ACR: American College of Rheumatology score; HAQ-DI: Health Assessment Questionnaire Disability Index; NS: not stated; PASI: Psoriasis Area and Severity Index; PsARC: Psoriatic Arthritis Response Criteria; SF-36: Short Form-36 Questionnaire. * Underlined outcome measures are the primary ones. † For safety analysis the intervention group included all patients randomized to infliximab and all patients randomized to placebo who entered early escape at Week 16 (n = 97 placebo and n = 150 infliximab[29]).

Table 2. Demographic characteristics of participants included in the randomized controlled trials.

Characteristic	Mease[24]		Genovese[25]		Mease[26]		Mease[27]		Antoni[28]		Antoni[29]	
	Placebo	Adalimumab	Placebo	Adalimumab	Placebo	Etanercept	Placebo	Etanercept	Placebo	Infliximab	Placebo	Infliximab
Age, yrs, mean ± SD	49.2 ± 11.1	48.6 ± 12.5	47.7 ± 11.3	50.4 ± 11.0	43.5	46.0	47.3	47.6	45.2 ± 9.7	45.7 ± 11.1	46 ± 11.3	47.1 ± 12.8
Sex, % male	54.9	56.3	51.0	56.9	60	53	45	57	57.7	57.7	51	71
PsA duration, yrs, mean ± SD	9.2 ± 8.7	9.8 ± 8.3	7.2 ± 7.0	7.5 ± 7.0	9.5	9.0	9.2	9.0	11.0 ± 6.6	11.7 ± 9.8	7.5 ± 7.8	8.4 ± 7.2
Ps duration, yrs, mean ± SD	17.1 ± 12.6	17.2 ± 12.0	13.8 ± 10.7	18.0 ± 13.2	17.5	19.0	19.7	18.3	19.4 ± 11.6	16.9 ± 10.9	NS	NS
RF-negative, %	90.1	89.4	98.0	80.4	NS	NS	96	91	100	100	100	100
CR protein, mg/dl (normal < 0.287), mean ± SD	1.4 ± 1.7	1.4 ± 2.1	1.6 ± 1.7	1.0 ± 1.0	NS	NS	NS	NS	31.1 ± 38.1	21.7 ± 27.0	23 ± 34	1.9 ± 21
Concomitant therapy, no (%)												
MTX	50 (30.9)	51 (33.8)	23 (46.9)	24 (47.1)	14 (47)	14 (47)	43 (41)	42 (42)	NS	NS	45 (45)	47 (47)
Corticosteroids	NS	NS	NS	NS	12 (40)	6 (20)	16 (15)	19 (19)	NS	NS	10 (10)	15 (15)
NSAID	NS	NS	NS	NS	23 (77)	20 (67)	86 (83)	89 (88)	NS	NS	73 (73)	71 (71)
TJC (0–68 joints), mean ± SD	25.8 ± 18.0	23.9 ± 17.3	29.3 ± 18.1	25.3 ± 18.3	NS	NS	NS	NS	20.4 ± 12.1	23.7 ± 13.7	25.1 ± 13.3	24.6 ± 14.1
SJC (0–66 joints), mean ± SD	14.3 ± 11.1	14.3 ± 12.2	18.4 ± 12.1	18.2 ± 10.9	NS	NS	NS	NS	14.7 ± 8.2	14.6 ± 7.5	14.4 ± 8.9	13.9 ± 7.9

MTX: Methotrexate; NS: not stated; Ps: psoriasis; PsA: psoriatic arthritis; RF: rheumatoid factor; SJC: swollen joint count; TJC: tender joint count.

ACR50, and ACR70 scores. Adalimumab, etanercept, and infliximab were all significantly more effective than placebo for all 3 ACR response thresholds. The pooled relative risks across all trials at 12–16 weeks were 4.35 (95% CI 3.24, 5.84) for ACR20 (Figure 2), 10.37 (95% CI 6.36, 16.93) for ACR50, and 16.51 (95% CI 6.74, 40.40) for ACR70. The individual relative risk for each treatment comparison is shown in Table 3. In the indirect analysis, there were no significant differences between the TNF-α inhibitors in achieving the ACR20 response (Table 4).

All 3 TNF-α inhibitors were also significantly more effective than placebo on the basis of the PsARC. The

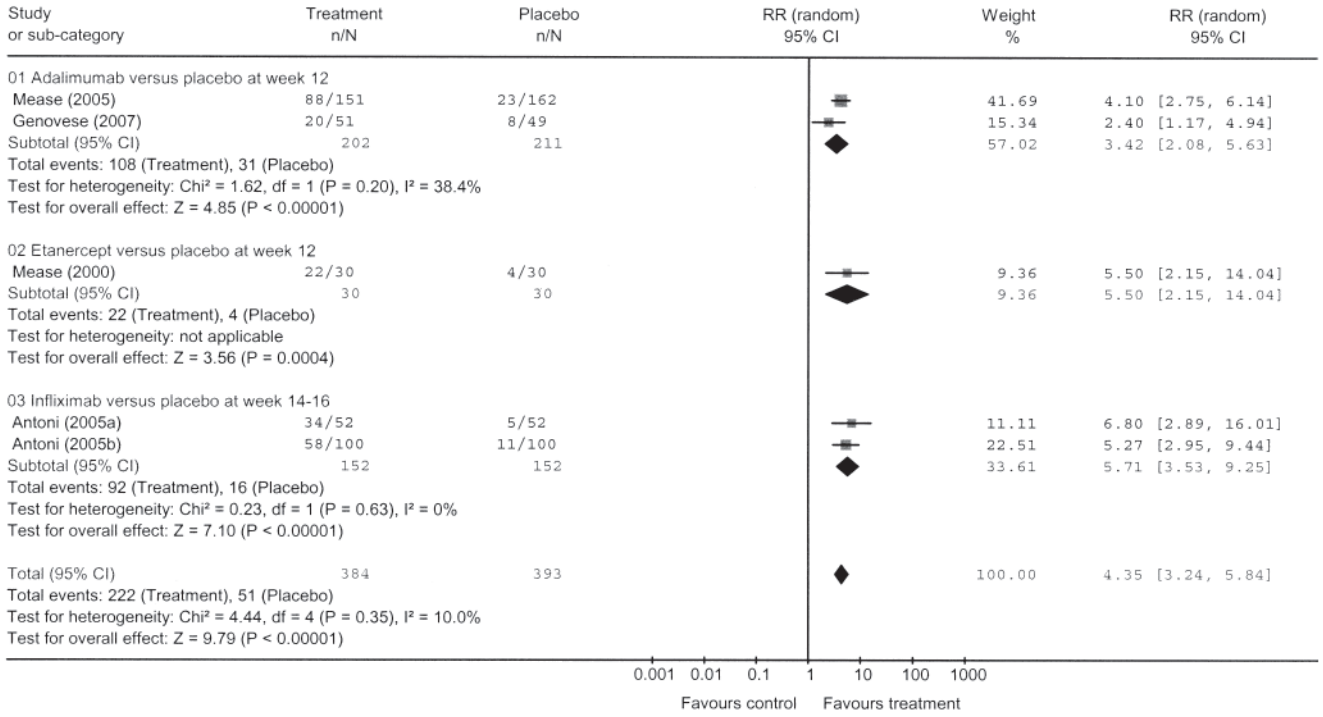

Figure 2. Relative risk (RR) for the proportion of patients achieving the American College of Rheumatology 20 (ACR20) response at 12–16 weeks comparing TNF-α inhibitors against placebo.

pooled RR across the 6 trials at 12–16 weeks was 2.60 (95% CI 2.22, 3.04). As shown in Table 3, two trials including 413 patients found that adalimumab was significantly more effective than placebo in achieving the PsARC at 12 weeks (RR 2.33; 95% CI 1.80, 3.01)[24,25]. It was also significantly more effective than placebo at 24 weeks (RR 2.64; 95% CI 1.93, 3.60)[24]. Two trials including 265 patients found that etanercept was significantly more effective than placebo in achieving PsARC; the pooled RR at Week 12 was 2.68 (95% CI 1.78, 4.04)[26,27]. Similarly, 2 trials compared infliximab against placebo in 304 patients, and the corresponding pooled RR for the proportion of patients achieving the PsARC at Weeks 14–16 was 3.03 (95% CI 2.27, 4.04)[28,29]. Indirect comparisons between the TNF-α inhibitors at 12–16 weeks did not identify any significant differences in PsARC response, as shown in Table 4.

Four RCT also reported on the mean percentage change in the HAQ-DI[24,25,28,29]. For adalimumab, the weighted mean difference in the percentage change in HAQ-DI at Week 12 was 26.67 (95% CI 20.13, 33.20)[24,25]. The pooled WMD for the percentage change in HAQ-DI in the 2 infliximab trials at 14 to 16 weeks was 56.06 (95% CI 42.07, 70.05)[28,29].

Psoriasis Area and Severity Index. Given the various degrees of severity of psoriasis in the patients included in the RCT, not all patients were screened for the PASI score. The pooled relative risks across all TNF-α inhibitors at 12–16 weeks were 5.50 (95% CI 2.53, 11.92) for PASI 50, 16.30 (95% CI 7.33, 36.28) for PASI 75, and 34.64 (95% CI 6.95, 172.57) for PASI 90. One of the adalimumab trials screened 69 patients for the PASI in each arm of the trial[24]. At 24 weeks, adalimumab was significantly more effective than placebo on the basis of PASI 50, 75, and 90 scores, as shown in Table 3. Similarly, etanercept was found to be significantly more effective than placebo on the basis of PASI 50 and 75 scores at 24 weeks, but no significant difference was detected on PASI 90 scores (RR 1.88, 95% CI 0.36, 9.90). The 2 trials that evaluated the use of infliximab screened 209 patients; the pooled RR at 14–16 weeks showed that infliximab was significantly more effective than placebo on PASI 50, 75, and 90 scores (Table 3)[28,29].

Quality of life. Only 3 trials included quality of life measures, and all used the Medical Outcome Study Short Form-36 questionnaire (SF-36)[25,30,31]. Adalimumab was found to be significantly more effective than placebo on the physical component of the SF-36; the WMD in response at 12 weeks was 5.54 (95% CI 0.64, 10.43) and 7.90 (95% CI 5.63, 10.17) at Week 24[24,25,32]. However, no significant differences were found in changes in the mental component scores; the WMD was 0.88 (95% CI –0.99, 2.75) at Week 12 and 1.20 (95% CI –1.06, 3.46) at Week 24. In contrast, infliximab was significantly better than placebo on the basis of both the mental and physical component scores at 14 weeks; the corresponding WMD were 5.00 (95% CI 2.16, 7.84) and 8.00 (95% CI 5.27, 10.73), respectively[29].

Safety and tolerability. There were no significant differences

Table 3. Relative risks (RR) and risk differences (RD) for the proportions of patients achieving PsARC, ACR, and PASI outcomes comparing TNF-α inhibitors against placebo.

Outcome Measure	TNF-α Inhibitor	No. of Trials	Time Point, wks	Achieved no./Total no. Intervention	Placebo	RR (95% CI)	RD (95% CI)	Test for Homogeneity I^2 (%)	p
PsARC	Adalimumab	2	12	120/202	54/211	2.33 (1.80, 3.01)*	0.34 (0.25, 0.43)*	0	0.66
	Adalimumab	1	24	91/151	37/162	2.64 (1.93, 3.60)*	0.37 (0.27, 0.48)*	—	—
	Etanercept	2	12	66/131	39/134	2.68 (1.78, 4.04)*	0.51 (0.30, 0.73)*	33.9	0.22
	Etanercept	1	24	71/101	24/104	3.05 (2.10, 4.42)*	0.47 (0.35, 0.59)*	—	—
	Infliximab	2	14–16	116/152	38/152	3.03 (2.27, 4.04)*	0.51 (0.42, 0.61)*	0	0.51
ACR20	Adalimumab	2	12	108/202	31/211	3.42 (2.08, 5.63)*	0.35 (0.14, 0.55)*	38.4	0.20
	Adalimumab	1	24	86/151	24/162	3.84 (2.59, 5.70)*	0.42 (0.33, 0.52)*	—	—
	Etanercept	1	12	22/30	4/30	5.50 (2.15, 14.04)*	0.60 (0.40, 0.80)*	—	—
	Etanercept	1	24	50/101	14/104	3.68 (2.17, 6.22)*	0.36 (0.24, 0.48)*	—	—
	Infliximab	2	14–16	92/152	16/152	5.71 (3.53, 9.25)*	0.50 (0.41, 0.59)*	0	0.63
ACR50	Adalimumab	2	12	67/202	8/211	8.71 (4.30, 17.66)*	0.29 (0.22, 0.36)*	0	0.70
	Adalimumab	1	24	59/151	10/162	6.33 (3.36, 11.92)*	0.33 (0.24, 0.42)*	—	—
	Etanercept	2	12	53/131	5/134	10.68 (4.40, 25.89)*	0.38 (0.26, 0.49)*	0	0.70
	Etanercept	1	24	37/101	4/104	9.52 (3.52, 25.75)*	0.33 (0.23, 0.43)*	—	—
	Infliximab	2	14–16	60/152	3/152	14.73 (5.11, 42.43)*	0.39 (0.26, 0.51)*	0	0.33
ACR70	Adalimumab	2	12	37/202	2/211	15.75 (4.44, 55.82)*	0.17 (0.12, 0.23)*	0	0.95
	Adalimumab	1	24	35/151	2/162	18.77 (4.59, 76.72)*	0.22 (0.15, 0.29)*	—	—
	Etanercept	2	12	15/131	0/134	14.75 (1.97, 110.51)*	0.11 (0.06, 0.17)*	0	0.63
	Etanercept	1	24	9/101	1/104	9.27 (1.20, 71.83)*	0.08 (0.02, 0.14)*	—	—
	Infliximab	2	14–16	30/152	1/152	19.21 (3.77, 97.87)*	0.21 (0.06, 0.35)*	0	0.67
PASI 50	Adalimumab	1	12	50/69	10/69	5.00 (2.77, 9.03)*	0.58 (0.45, 0.71)*	—	—
	Adalimumab	1	24	52/69	8/69	6.50 (3.34, 12.64)*	0.64 (0.51, 0.76)*	—	—
	Etanercept	1	12	8/19	4/19	2.00 (0.72, 5.53)	0.21 (–0.08, 0.50)	—	—
	Etanercept	1	24	31/66	11/62	2.65 (1.46, 4.80)*	0.29 (0.14, 0.45)*	—	—
	Infliximab	2	14–16	90/105	8/104	9.70 (4.90, 19.23)*	0.86 (0.54, 1.19)*	1.3	0.31
PASI 75	Adalimumab	1	12	34/69	3/69	11.33 (3.65, 35.17)*	0.45 (0.32, 0.58)*	—	—
	Adalimumab	1	24	41/69	1/69	41.00 (5.80, 289.75)*	0.58 (0.46, 0.70)*	—	—
	Etanercept	1	12	5/19	0/19	11.00 (0.65, 186.02)	0.26 (–0.06, 0.47)	—	—
	Etanercept	1	24	15/66	2/62	7.05 (1.68, 29.65)*	0.20 (0.08, 0.31)*	—	—
	Infliximab	2	14–16	68/105	2/104	27.03 (7.88, 92.74)*	0.63 (0.53, 0.73)*	0	0.93
PASI 90	Adalimumab	1	12	21/69	0/69	43.00 (2.66, 696.04)*	0.30 (0.19, 0.41)*	—	—
	Adalimumab	1	24	29/69	0/69	59.00 (3.68, 946.75)*	0.42 (0.30, 0.54)*	—	—
	Etanercept	1	24	4/66	2/62	1.88 (0.36, 9.90)	0.03 (–0.04, 0.10)	—	—
	Infliximab	2	14–16	42/105	0/104	31.10 (4.35, 222.07)*	0.40 (0.31, 0.50)*	0	0.38

ACR: American College of Rheumatology score; PASI: Psoriatic Area Severity Index. * $p < 0.05$.

Table 4. Indirect comparisons of TNF-α inhibitors at 12–16 weeks.

Outcome Measure	Comparison	Indirect RR (95% CI)
Efficacy		
ACR 20	Adalimumab vs etanercept	0.63 (0.22, 1.81)
	Adalimumab vs infliximab	0.60 (0.30, 1.20)
	Etanercept vs infliximab	0.96 (0.33, 2.76)
PsARC	Adalimumab vs etanercept	1.35 (0.67, 2.73)
	Adalimumab vs infliximab	0.77 (0.53, 1.13)
	Etanercept vs infliximab	0.57 (0.28, 1.17)
Safety		
Serious AE	Adalimumab vs etanercept	0.61 (0.12, 3.03)
	Adalimumab vs infliximab	0.52 (0.14, 2.01)
	Etanercept vs infliximab	0.64 (0.14, 2.96)

ACR: American College of Rheumatology score; AE: Adverse event; PsARC: Psoriatic Arthritis Response Criteria; RR: relative risk.

in overall withdrawal rates in comparisons between those receiving adalimumab or infliximab against placebo, but significantly fewer patients withdrew from treatment with etanercept compared with placebo (RR 0.24, 95% CI 0.12, 0.49), as shown in Table 5. The majority of withdrawals in those assigned to placebo resulted from an unsatisfactory therapeutic effect. There were also no significant differences between any of the TNF-α inhibitors and placebo in withdrawals due to adverse events, the proportions of patients experiencing serious adverse events, or upper respiratory tract infections (Table 5). Indirect analysis found that there were no significant differences between TNF-α inhibitors in the proportion of patients experiencing serious adverse events (Table 4).

Four trials including 678 patients reported the proportions of patients experiencing injection site reactions[24-27].

Table 5. Relative risk (RR) and risk differences (RD) for the proportion of patients experiencing adverse events (AE) comparing TNF-α inhibitors against placebo.

Outcome Measure	Comparison vs Placebo	No. of Trials	Achieved no./Total no. Intervention	Placebo	RR (95% CI)	RD (95% CI)	Test for Homogeneity I^2 (%)	p
Withdrawal for any reason								
	Adalimumab	2	11/202	15/211	0.83 (0.39, 1.74)	–0.02 (–0.07, 0.02)	0	0.32
	Etanercept	2	8/131	36/134	0.24 (0.12, 0.49)*	–0.19 (–0.29, –0.09)*	0	0.58
	Infliximab	1	3/5	2/52	1.50 (0.26, 8.61)	0.02 (–0.06, 0.10)	—	—
	Pooled	5	22/358	53/397	0.48 (0.20, 1.18)	–0.07 (–0.15, 0.01)	53.1	0.07
Withdrawal due to AE								
	Adalimumab	2	4/202	2/211	1.98 (0.35, 11.28)	0.01 (–0.01, 0.03)	0	0.50
	Etanercept	1	1/101	1/104	1.03 (0.07, 16.24)	0.00 (–0.02, 0.02)	—	—
	Infliximab†	2	8/202	2/149	2.90 (0.60, 13.96)	0.03 (–0.01, 0.06)	0	0.68
	Pooled	5	13/535	5/494	2.14 (0.73, 6.27)	0.01 (0.00, 0.03)	0	0.90
Serious AE	Adalimumab	2	6/202	9/211	0.70 (0.25, 1.94)	–0.01 (–0.05, 0.02)	0	0.73
	Etanercept	2	4/131	5/134	0.86 (0.25, 3.01)	–0.01 (–0.05, 0.04)	0	0.52
	Infliximab†	2	14/202	7/149	1.35 (0.56, 3.27)	0.01 (–0.03, 0.02)	0	0.82
	Pooled	5	24/535	21/494	0.98 (0.55, 1.77)	0.00 (–0.03, 0.02)	0	0.91
Upper respiratory tract infections								
	Adalimumab	2	26/202	28/211	0.98 (0.57, 1.69)	0.00 (–0.07, 0.07)	7.0	0.30
	Etanercept	2	29/131	28/134	1.16 (0.56, 2.39)	0.03 (–0.11, 0.18)	40.7	0.19
	Infliximab†	2	16/202	19/149	0.56 (0.22, 1.42)	–0.06 (–0.12, 0.00)	19.0	0.27
	Pooled	6	71/535	75/494	0.91 (0.65, 1.28)	–0.02 (–0.07, 0.02)	12.8	0.33
Injection site reactions								
	Adalimumab	2	16/202	11/211	1.44 (0.65, 3.17)	0.03 (–0.01, 0.08)	10.5	0.29
	Etanercept	2	42/131	10/134	4.27 (2.25, 8.13)*	0.23 (0.14, 0.33)*	0	0.73
	Pooled	4	58/333	21/345	2.48 (1.16, 5.29)*	0.11 (0.02, 0.25)*	49.5	0.11
Infusion reactions	Infliximab†	2	15/202	11/149	1.03 (0.48, 2.20)	0.00 (–0.05, 0.06)	0	0.63

* $p < 0.05$. † For safety analysis of Antoni, *et al* : the intervention group included all patients randomized to infliximab and all patients randomized to placebo who entered the early escape at Week 16 (n = 97 placebo and n = 150 infliximab[29]).

The pooled RR was 2.48 (95% CI 1.16, 5.29) indicating that anti-TNF injections were more likely to cause reactions (Table 5). Reactions were not significantly more likely with adalimumab (RR 1.44, 95% CI 0.65, 3.17)[24,25], but were with etanercept (RR 4.27, 95% CI 2.25, 8.13)[27,33]. There were no significant differences in the proportions of patients experiencing infusion reactions with infliximab compared against placebo (RR 1.03, 95% CI 0.48, 2.20)[28,29]. Five trials including 922 patients monitored the incidence of malignancies during treatment[24,25,27-29]. Only one patient treated with placebo developed a basal cell carcinoma of the skin[29].

DISCUSSION

In this systematic review, the TNF-α inhibitors adalimumab, etanercept, and infliximab were found to be highly effective, achieving significant improvements in PsARC, ARC, and PASI scores, as well as showing improvements in quality of life. In contrast, when other disease-modifying agents, including sulfasalazine and gold therapy, have been assessed in PsA, few or no benefits have been found[8]. Only modest differences were apparent in the results obtained from the different TNF-α inhibitors, and there were no important added risks associated with their short-term use. The main differences in tolerability related to higher rates of injection site reactions reported in patients receiving etanercept compared to placebo. We found no significant differences in infusion reactions in those receiving infliximab. In addition, indirect comparisons did not demonstrate any significant differences in response between any of the TNF-α inhibitors for specific efficacy or safety outcomes.

An important consideration for the use of TNF-α inhibitors in PsA is the lack of longterm studies to assess rare but potentially serious adverse events. In an open-label 54-week study that used infliximab for treatment of PsA, there were no important adverse events, severe infections, or infusion reactions[34]. However, Bongartz, *et al* recently published a metaanalysis of 9 RCT of infliximab and adalimumab in patients with rheumatoid arthritis and reported that rates of malignancies and serious infections were significantly higher in patients receiving TNF-α inhibitors compared to placebo[35]. Similar concerns arise when using these agents for PsA over extended periods, as many of these patients will have been exposed to other treatments for psoriasis, such as PUVA (psoralen plus UVA phototherapy), with recognized risks of cancer[36]. In the short term, we found no differences in rates of upper respiratory tract infections between TNF-α inhibitors and placebo, and only one malignancy was detected in a placebo-treated patient.

However, the lack of longterm controlled studies severely compromises any comparative safety assessment, and is an important area for future research to assess the longterm risk-benefit profile of these biological agents in PsA. Open-label extensions of some of the studies included in this review have shown that similar efficacy outcomes can be achieved up to 24 weeks for adalimumab[24,25], 12 months for etanercept[27], and 24 months for infliximab[37-39].

Our systematic review used a range of clinically relevant outcome measures and focused on the direct and indirect comparison of TNF-α inhibitors. To date, there have been no direct head-to-head trials of TNF-α inhibitors in the treatment of PsA, and this would be an area for future research to help guide clinical decisions about choice of treatment. In this review, the different trials used different agents, routes of administration, and evaluation timepoints that ranged from 4 to 24 weeks from baseline. We accommodated this diversity by stratifying the analyses according to the type of the intervention and the evaluation timepoint. However, adverse events were reported only at the end of each of the trials rather than at specific timepoints. Given that we were unable to determine when specific adverse events occurred, we were forced to pool response rates across all timepoints, which resulted in some comparisons having moderately high I^2 values for heterogeneity.

Even though there have been fewer RCT in PsA than in rheumatoid arthritis and psoriasis historically, these trials have shown significant discrimination in multiple domains of interest including joints, skin, physical function, quality of life, and radiographic outcomes. PsA is a chronic condition that requires continuous treatment for long periods. The included efficacy trials were conducted over relatively short periods in highly selected populations. Given the likely longterm use of these agents in clinical practice, there is a need for longitudinal observational studies with sufficient numbers of patients to investigate the longterm comparative safety of these agents in the management of PsA.

REFERENCES

1. Leonard DG, O'Duffy JD, Rogers RS. Prospective analysis of psoriatic arthritis in patients hospitalized for psoriasis. Mayo Clin Proc 1978;53:511-8.
2. Gladman DD. Psoriatic arthritis. Baillieres Clin Rheumatol 1995;9:319-29.
3. Shbeeb M, Uramoto KM, Gibson LE, O'Fallon WM, Gabriel SE. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982-1991. J Rheumatol 2000;27:1247-50.
4. Gladman DD, Stafford-Brady F, Chang CH, Lewandowski K, Russell ML. Longitudinal study of clinical and radiological progression in psoriatic arthritis. J Rheumatol 1990;17:809-12.
5. Gladman DD, Helliwell P, Mease PJ, Nash P, Ritchlin C, Taylor W. Assessment of patients with psoriatic arthritis: a review of currently available measures. Arthritis Rheum 2004;50:24-35.
6. Husted JA, Gladman DD, Farewell VT, Cook RJ. Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. Arthritis Rheum 2001;45:151-8.
7. Javitz HS, Ward MM, Farber E, Nail L, Vallow SG. The direct cost of care for psoriasis and psoriatic arthritis in the United States. J Am Acad Dermatol 2002;46:850-60.
8. Jones G, Crotty M, Brooks P. Interventions for treating psoriatic arthritis. Cochrane Database Syst Rev 2000; CD000212.
9. Kaltwasser JP, Nash P, Gladman D, et al. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. Arthritis Rheum 2004;50:1939-50.
10. Ettehadi P, Greaves MW, Wallach D, Aderka D, Camp RD. Elevated tumour necrosis factor-alpha (TNF-alpha) biological activity in psoriatic skin lesions. Clin Exp Immunol 1994;96:146-51.
11. Ritchlin CT. Pathogenesis of psoriatic arthritis. Curr Opin Rheumatol 2005;17:406-12.
12. Soriano ER, McHugh NJ. Therapies for peripheral joint disease in psoriatic arthritis. A systematic review. J Rheumatol 2006;33:1422-30.
13. Clegg DO, Reda DJ, Mejias E, et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. Arthritis Rheum 1996;39:2013-20.
14. Fransen J, Antoni C, Mease PJ, et al. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: Analysis of data from randomized, controlled trials of two TNF inhibitors. Ann Rheum Dis 2006;65:1373-8.
15. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.
16. Ashcroft DM, Li Wan Po A, Williams HC, Griffiths CEM. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. Br J Dermatol 1999;141:185-91.
17. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions 4.2.5. Updated May 2005. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons Ltd.; 2005.
18. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1-12.
19. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719-48.
20. Sterne JAC, Bradburn MJ, Egger M. Meta-analysis in Stata. In: Egger M, Davey Smith G, Altman DJ, editors. Systematic reviews in health care: meta-analysis in context. 2nd ed. London: BMJ Books; 2001:347-69.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
23. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683-91.
24. Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2005;52:3279-89.
25. Genovese MC, Mease PJ, Thomson GT, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. J Rheumatol 2007;34:1040-50.
26. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet 2000;356:385-90.
27. Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease

progression. Arthritis Rheum 2004;50:2264-72.
28. Antoni CE, Kavanaugh A, Kirkham B, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum 2005;52:1227-36.
29. Antoni C, Krueger GG, de Vlam K, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis 2005;64:1150-7.
30. Ware JE Jr, Sherbourne CD. The MOS 36-item Short-form Health Survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
31. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. Health Qual Life Outcomes 2003;1:20.
32. Gladman DD, Mease PJ, Cifaldi MA, Perdok RJ, Sasso E, Medich J. Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial. Ann Rheum Dis 2007;66:163-8.
33. Mease PJ. Cytokine blockers in psoriatic arthritis. Ann Rheum Dis 2001;60 Supp 3:iii37-40.
34. Antoni C, Dechant C, Hanns-Martin Lorenz PD, et al. Open-label study of infliximab treatment for psoriatic arthritis: clinical and magnetic resonance imaging measurements of reduction of inflammation. Arthritis Rheum 2002;47:506-12.
35. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275-85.
36. Raiss M, Templier I, Beani JC. Skin cancer and psoralen plus UVA: a retrospective study of 106 patients exposed to a great number of PUVA treatments. Ann Dermatol Venereol 2004;131:437-43.
37. Kavanaugh A, Antoni CE, Gladman D, et al. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. Ann Rheum Dis 2006;65:1038-43.
38. Rinaldi F, Provenzano G, Termini A, Spinello M, La SF. Long term infliximab treatment for severe psoriatic arthritis: evidence of sustained clinical and radiographic response. Ann Rheum Dis 2005;64:1375-6.
39. Kavanaugh A, Antoni C, Krueger GG, et al. Infliximab improves health-related quality of life and physical function in patients with psoriatic arthritis. Ann Rheum Dis 2006;65:471-7.